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Cord blood ischemia-modified albumin: Is it associated with abnormal Doppler findings in complicated pregnancies and predictive of perinatal asphyxia?

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Abstract

Aim: To evaluate the significance of the cord blood ischemia-modified albumin (IMA) level as a diagnostic marker for perinatal asphyxia and to determine the associations of IMA levels with the complexity of pregnancy and abnormal Doppler findings, regardless of perinatal asphyxia.

Methods: This prospective study included 169 newborns, sixteen of whom had perinatal asphyxia and 33 who were from complicated pregnancies. Doppler measurements were obtained from the uterine, umbilical and middle cerebral arteries, and the cerebro/placental ratio (C/P). IMA was measured by means of commercially available ELISA kits and was expressed as picomoles per milliliter.

Results: Ischemia-modified albumin levels were significantly higher in neonates of complicated pregnancies as compared to uncomplicated pregnancies ($P < 0.0001$). They were higher in newborns with perinatal asphyxia as compared to healthy controls ($P = 0.015$). The C/P ratio-pulsatility index (PI) showed a significant difference between normal and complicated pregnancies without perinatal asphyxia ($P < 0.0001$). IMA levels were significantly increased in cases with abnormal C/P ratio-PI.

Conclusions: Elevated cord blood IMA levels may be accepted as a useful marker in perinatal asphyxia. Abnormal Doppler examinations are associated with elevated IMA levels in complicated pregnancies.

Key words: Doppler imaging, ischemia-modified albumin, perinatal asphyxia, pregnancy complication, prenatal care.

Introduction

Neonatal asphyxia is a serious concern that may lead to neonatal death and long-term neurodevelopmental problems; an insufficient supply of oxygen before, during or just after delivery was assumed to be the cause. While the incidence is approximately 1 in 1000 live births in developed countries, it is probably much more common in developing countries.[1] Therefore, different biochemical and biophysical tests have been investigated for the prediction of fetuses at risk for hypoxic brain damage and hopefully to prevent this damage, but many of them have remained limited.[2]

In recent clinical studies, it has been found that ischemia-modified albumin (IMA) is a new biochemical marker for the early diagnosis of myocardial ischemic events and cerebrovascular accidents.[3,4] IMA is a modification of human serum albumin (HSA). N-terminal amino acids of HSA temporarily bind to transitional metals such as cobalt, nickel and copper.[5] Hypoxia, acidosis or ischemia leads to a change on this

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region and reduce the binding capacity of HSA to these metals. The resulting molecule is called IMA.[5] IMA rapidly increases within 5 to 10 min after the ischemic event and remains high for 30 min. It returns to baseline 12 h after the ischemia event, but if the ischemic event persists, it continues to rise.[3]

Doppler ultrasound imaging is presently used for management and follow-up in pregnancies complicated with a variety of common diseases such as hypertension and diabetes mellitus, in which blood flow through the placenta is compromised.[6] In response to hypoxia resulting from placental insufficiency, fetal compensatory mechanisms redistribute blood flow toward essential fetal organs.[6] The early stage of this redistribution results in increased blood flow to the brain and is detected with increased resistance of the umbilical artery (UA) and decreased resistance of the middle cerebral artery (MCA) at Doppler examination. The cerebral/placental ratio (C/P ratio) becomes less than one. It has been called the 'brain sparing effect' and it has been suggested that the C/P ratio alone was a more precise index than others.[7] However, the relationship of serum IMA levels, as a hypoxia-related marker, with abnormal Doppler findings has never been investigated.

In these considerations, the primary aim of this study was to evaluate the diagnostic significance of assessing cord blood IMA level in newborns exposed to perinatal asphyxia. We also aimed to determine whether cord blood IMA levels showed a difference between newborns from complicated pregnancies and healthy controls, and to investigate the association of IMA levels with abnormal Doppler findings identified just before delivery in newborns without perinatal asphyxia.

Methods

This prospective, case-control study was performed between August 2009 and May 2011, and was approved by the local research ethics committee. All mothers included in the study provided signed, informed consent before recruitment. A total of 169 newborns were included in the present study. One hundred and thirty-six of them were born after normal pregnancies and 33 were born from pregnancies complicated by pre-eclampsia, gestational diabetes mellitus (GDM) and/or intrauterine growth restriction (IUGR). Sixteen newborns of these 169 patients were diagnosed as exposed to perinatal asphyxia by previously defined American Academy of Pediatrics and Committee and American College of Obstetrics and Gynecology criteria.[8]

Pre-eclampsia was defined as hypertension (systolic blood pressure ≥140 mmHg after 24 weeks' gestation) plus proteinuria (urine protein concentration ≥300 mg in a 24-h urine sample).[9] A diagnosis of GDM was made using a sequential model of universal screening with a 50-g one-hour glucose challenge test, followed by a diagnostic 100-g three-hour oral glucose tolerance test for women with a positive screening test.[10] IUGR was defined as a birth weight below the 10th percentile for gestational age.[11] Amniotic fluid was diminished in all cases of IUGR. For the evaluation of amniotic fluid, the amniotic fluid index was defined as diminished if it was less than 5 cm.[12] The inclusion criteria included normal fetal anatomy and singleton pregnancies with gestational age correctly dated by the last menstrual period and/or sonographic examination prior to 20 weeks' gestation. The exclusion criteria were chorioamnionitis, abnormal fetal karyotype, current smoker, neonatal hypoalbuminemia (serum albumin <2.5 g/dL) and elevated levels of high sensitivity C-reactive protein (hs-CRP) in newborns (>5.5 mg/L).

The Doppler examination was performed only after 33 weeks' gestation because extreme prematurity is the main cause of adverse perinatal outcomes and it would be difficult to comment on Doppler findings because of a relatively broad range of normal and abnormal indices before these gestational weeks.[13] Therefore, this study was performed in pregnancies between 33 and 41 weeks' gestation. Fetal biometry was measured and weight calculated by the Hadlock formula.[14] Also, antenatal Doppler findings of newborns with clinical evidence of asphyxia were not included in the statistical analysis.

All Doppler examinations and ultrasound measurements were performed by one of the two investigators (S. G. and E. O.) using a Voluson 730 ultrasound machine equipped with a 3.5-MHz convex transabdominal probe (GE Medical Systems, Milwaukee, WI, USA). During the examination, Doppler measurements of the uterine artery (UtA), UA and MCA were obtained using previously described methods.[15,16] Then the systolic–diastolic ratio (S/D), pulsatility index (PI = peak systolic velocity – end diastolic velocity/mean velocity) and resistance index (RI = peak systolic velocity – end diastolic velocity/peak systolic velocity) were calculated for each artery.[12,15,16] A minimum of three consecutive waveforms of similar configurations were

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used for evaluation and the mean value was recorded. A decrease of >2 SD in these indices of MCA was accepted as abnormal, but an elevation of >2 SD in these indices of UtA or UA was considered abnormal.[12] The C/P ratio was calculated by MCA-PI/UA-PI and a ratio of <1.08 was considered abnormal.[17] Doppler ultrasonography was performed in the last six hours prior to delivery because the IMA level returned to normal after about six hours following reperfusion.

Four milliliters of venous blood sample from the umbilical cord was collected in non-heparinized tubes by direct venipuncture of the umbilical vein following double clamping of the umbilical cords just after delivery of the neonate. Blood samples were immediately centrifuged after clotting. The supernatant serum was stored at –80°C until assay.

Samples were allowed to clot for 30 min and then centrifuged for 10 min at 3500 rpm. The aliquots of supernatants were stored at –80°C until testing. Frozen samples were mixed thoroughly after thawing and recentrifuged before analysis. Samples with more than a trace of hemolysis were discarded. All serum samples were diluted 400-fold with 0.02 M PBS before analysis.

Expressions at the protein level for IMA were determined by means of commercially available ELISA kits and performed according to the manufacturer's instructions (USCN Life Science, Wuhan, China). The absorbance was measured at 450 nm using a microplate reader. Quantifications were achieved by the construction of standard curves using known concentrations of IMA and the results were expressed in picomoles per milliliter (pmol/mL).[3]

Statistical analysis was performed using the SPSS version 15.0 statistical package (SPSS, Chicago, IL, USA). Normal distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Differences between cases and controls were tested for significance using the χ^2-test (or Fischer's exact test) for categorical variables. Student's *t*-test was used for normally distributed variables in the analysis of continuous variables and the Mann–Whitney U-test was used for non-normally distributed variables. The data were indicated as median and range for non-normally distributed variables. Pearson and Spearman correlation coefficients were used for the analysis of correlation for continuous normally and non-normally distributed variables, respectively. Logistic regression modeling was conducted with the use of a forward conditional approach, including variables that showed statistically significant differences with univariate comparisons and other factors with potential clinical significance. A receiver operating characteristic (ROC) curve was constructed, and sensitivity and specificity were calculated based on the best cut-off. The optimal cut-off for IMA was determined from the ROC curve as the point nearest to the upper left corner. Values of $P < 0.05$ were considered to indicate a statistically significant difference.

Table 1 Complicated pregnancy group

Condition	*n*	%
Pre-eclampsia	2	6.1
Diabetes mellitus	21	63.6
Insulin-dependent	5	
No insulin	16	
IUGR	5	15.2
GDM + pre-eclampsia	2	6.0
Pre-eclampsia + IUGR	3	9.1
Total	33	100.0

GDM, gestational diabetes mellitus; IUGR, intrauterine growth restriction.

Results

Thirty-three (19.5%) of a total of 169 neonates were born in complicated pregnancies (Table 1). They had a lower birth weight when compared with neonates in the control group, but no differences were found in other clinical and demographic characteristics between these groups (Table 2). Their mean cord blood serum IMA levels were significantly elevated compared to those from uncomplicated pregnancies ($P < 0.0001$). The distribution of serum IMA levels between the groups is shown in Figure 1.

Perinatal asphyxia was diagnosed in a total of 16 (9.4%) neonates. In these cases, the mean birth weight and the rate of epidural anesthesia during delivery were significantly lower than the controls. Fifteen of the cases required resuscitation, while it was not required in the control group (Table 3). The cord blood serum IMA levels were also higher in newborns with perinatal asphyxia as compared to healthy controls, and a statistical significant difference was observed ($P = 0.015$). For both groups, the mean serum IMA levels were elevated in neonates from cesarean sections compared to those from vaginal deliveries, regardless of the presence of asphyxia or a complicated pregnancy, but it was not statistically significant (214.45 pmol/mL [SE: 21.3 pmol/mL] vs 174.81 pmol/mL [SE: 9.2 pmol/mL], respectively).

We also performed a multiple logistic regression to determine how differences in the IMA levels are

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Table 2 Clinical and demographic features of complicated pregnancies compared with the control group

	Complicated $n = 33$ (%)	Non-complicated $n = 136$ (%)	*P*-value
Maternal age (years)†	30.6 ± 6.6	29.7 ± 4.4	0.343
Gravida‡	1.9 ± 0.1	1.9 ± 0.2	0.997
Parity‡	0.6 ± 0.8	0.4 ± 0.6	0.300
Birthweight (g)‡	2988.93 ± 102.52	3312.08 ± 37.97	0.001
Gestational age (weeks)†	38.4 ± 1.1	38.7 ± 1.1	0.285
Mode of delivery			0.861
Vaginal	26 (78.8)	109 (80.1)	
C/S	7 (21.2)	27 (19.9)	
Anesthesia			0.739
Regional	27 (81.8)	118 (86.8)	
General	4 (12.1)	11 (8.1)	
None	2 (6.1)	7 (5.1)	
Fetal gender			0.876
Male	17 (51.5)	68 (50.0)	
Female	16 (48.5)	68 (50.0)	
Presence of asphyxia	4 (12.1)	12 (8.8)	0.562
Neonatal resuscitation	4 (12.1)	11 (8.1)	0.465
IMA (pmol/mL)‡	264.9 ± 8.7	162.9 ± 19.3	<0.0001

†Mean ± standard deviation (SD). ‡Mean ± standard error (SE). C/S, cesarean section; IMA, ischemia-modified albumin.

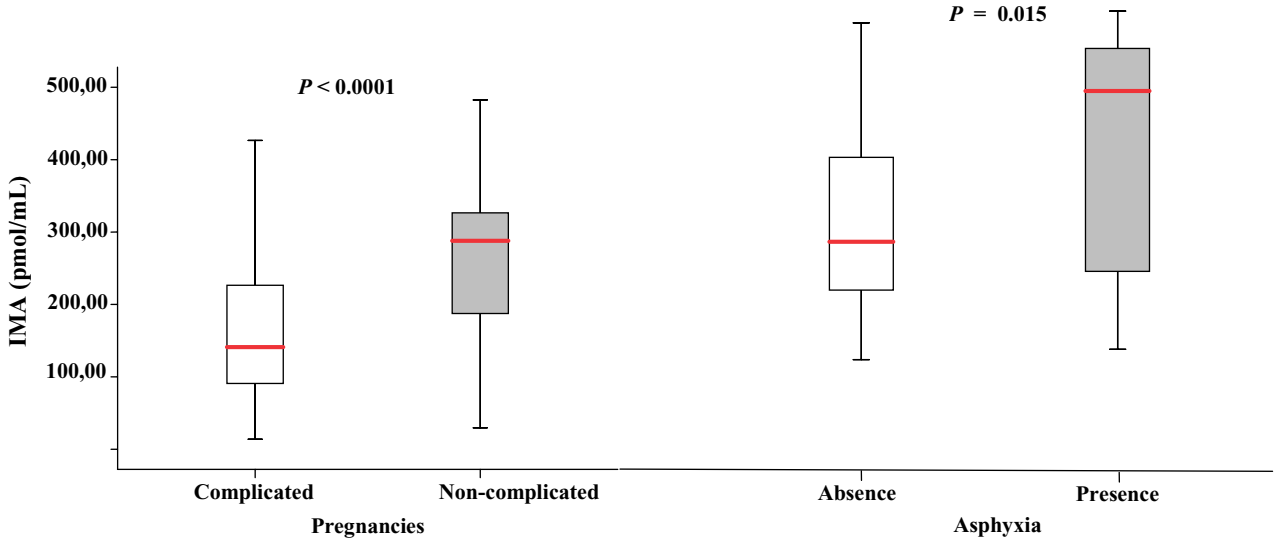


Figure 1 Cord blood serum ischemia-modified albumin (IMA) levels between the study groups.

affected by parameters such as birth weight. We observed that differences in the IMA levels were sustained in this model for neonates of complicated and asphyctic groups ($P < 0.001$, OR: 1.007 [95% CI, 1.003–1.01] and $P = 0.019$, OR: 1.16 [95% CI, 1.11–1.2], respectively).

We also investigated normal and complicated pregnancies without perinatal asphyxia according to their mean Doppler parameters (Table 4). The mean C/P ratio-PI showed a significant difference between these groups ($P < 0.0001$). Also, in complicated pregnancies, the percentage of abnormal C/P ratio-PI was significantly higher than in those of the control group ($P < 0.0001$). According to the C/P ratio-PI and UtA-PI indices, the neonatal cord blood IMA levels were significantly increased in cases with abnormal test results (Table 5). The neonatal IMA levels did not significantly correlate with their antenatal Doppler parameters,

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Table 3 Comparison of the clinical features of the neonates with perinatal asphyxia and non-asphyctic neonates

	Present $n = 16$ (%)	Absent $n = 153$ (%)	*P*-value
Maternal age (years)	33 (23–40)	29 (17–41)	0.171
Gravida	2 (1–6)	2 (1–6)	0.207
Birthweight (g)	2745 (1700–3600)	3290 (1550–4400)	<0.0001
Gestational age (weeks)	38.5 (33.0–40.0)	38.8 (34.0–41.0)	0.213
Mode of delivery			0.743
Vaginal	12 (75.0)	123 (80.4)	
C/S	4 (25.0)	30 (19.6)	
Anesthesia			<0.0001
Regional	8 (50.0)	137 (89.5)	
General	4 (25.0)	11 (7.2)	
None	4 (25.0)	5 (3.3)	
Fetal gender			0.980
Male	8 (50.0)	77 (50.3)	
Female	8 (50.0)	76 (49.7)	
Neonatal resuscitation	15 (93.8)	–	<0.0001
IMA (pmol/mL)	332.0 (26.0–426.5)	153.3 (13.8–482.4)	0.015

C/S, cesarean section; IMA, ischemia-modified albumin.

Table 4 Distribution of antenatal Doppler findings in 153 newborns with no clinical evidence of asphyxia and comparison with complicated and uncomplicated pregnancies

	Complicated $n = 29$ (%)	Non-complicated $n = 124$ (%)	*P*-value
MCA-PI	1.3 ± 0.3	1.5 ± 0.5	0.059
MCA-RI	0.72 ± 0.09	0.75 ± 0.10	0.207
MCA-S/D	4.1 ± 1.4	4.3 ± 1.7	0.396
UA-PI	0.8 ± 0.1	0.9 ± 0.9	0.515
UA-RI	0.56 ± 0.06	0.55 ± 0.10	0.543
UA-S/D	2.6 ± 0.5	2.5 ± 1.7	0.706
UtA-PI	0.9 ± 0.4	0.8 ± 0.4	0.157
UtA-RI	0.53 ± 0.11	0.50 ± 0.13	0.272
UtA-S/D	2.3 ± 0.8	2.2 ± 0.7	0.373
C/P Ratio-PI	1.10 ± 0.04	2.04 ± 0.18	<0.0001
Normal	9 (31.0)	108 (87.1)	
Abnormal	20 (69.0)	16 (12.9)	<0.0001†

†χ^2-test. C/P, cerebro/placental; MCA, middle cerebral artery; PI, pulsatility index; RI, resistance index; S/D, systolic–diastolic ratio; UA, umbilical artery; UtA, uterine artery.

except for UA-PI ($r = 0.205$, $P = 0.011$); however, we determined that they were adversely correlated with the birth weights and this correlation was statistically significant ($r = -0.187$, $P = 0.015$) (Fig. 2). The mean IMA levels were not different between 13 (7.7%) of the 169 newborns born at <37 weeks' gestation and 156 (92.3) of the newborns born at ≥37 weeks' gestation (179.4 ± 8.5 [SE] vs 222.9 ± 43.32 [SE], respectively).

The ROC curve of IMA for the prediction of neonatal asphyxia is shown in Figure 3. Accordingly, the area under curve was 0.685 ± 0.088 SE ($P = 0.015$; 95% CI, 0.51–0.85). The optimum diagnostic cut-off value maximizing sensitivity and specificity was detected to be 169.45 pmol/mL, with a sensitivity of 68% and a specificity of 58%.

Discussion

To our knowledge, the present study is the most extensive report evaluating neonatal cord blood IMA levels in clinical evidence of perinatal asphyxia. We also described the relationship between IMA levels and pregnancy-related disorders that may be associated with hypoxia and oxidative stress in newborns.

IMA is a modification of human serum albumin and it results from oxidative stress and concurrently produced superoxide free oxygen radicals that occur during ischemic events, regardless of tissue specificity.[3,5] It was accepted as a highly specific marker for myocardial ischemia and it has been indicated that the level of IMA remained high during the presence of ischemia.[3] There were also many reports showing its relationship with various ischemia-related conditions, such as acute coronary syndrome.[4] Recently, in two studies among normal pregnancies, it has been demonstrated that maternal serum IMA levels increased to supra-physiological levels in the first trimester of pregnancy compared to non-pregnant controls, and these levels continued to rise from the first trimester to the third trimester.[18,19] In previous reports, it has been clearly demonstrated that pre-eclampsia is a disease

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Table 5 Relationship of cord blood ischemia-modified albumin (IMA) levels with antenatal abnormal Doppler findings in non-asphyxia newborns

	MCA-PI		*P*	UA-PI		*P*	UtA-PI‡		*P*	C/P Ratio-PI‡		*P*
	Normal (n = 128)	Abnormal (n = 25)		Normal (n = 137)	Abnormal (n = 16)		Normal (n = 86)	Abnormal (n = 67)		Normal (n = 117)	Abnormal (n = 36)	
IMA (pmol/mL)	152.6 (23.1–482.4)	153.3 (13.8–482.4)	0.606	143.7 (13.8–461.4)	178.7 (23.6–482.4)	0.100	157.1 (±10.5)	196.4 (±13.3)	0.02†	162.5 (±9.3)	212.7 (±17.7)	**0.015†**

†Student *t*-test. ‡Mean ± standard error (SE). C/P, cerebro/placental; MCA, middle cerebral artery; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery.

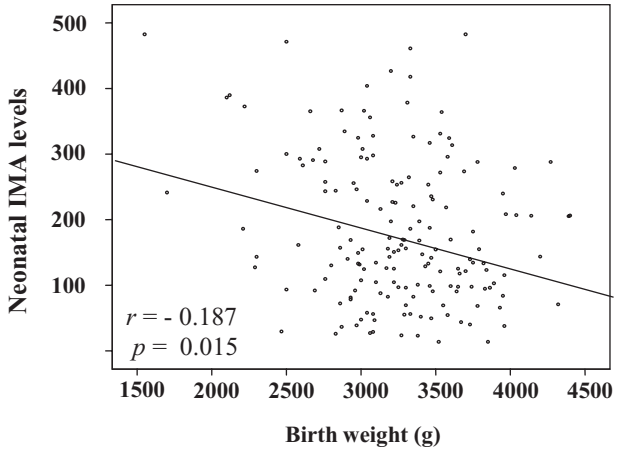


Figure 2 Correlation of neonatal serum ischemia-modified albumin (IMA) levels with birth weights.

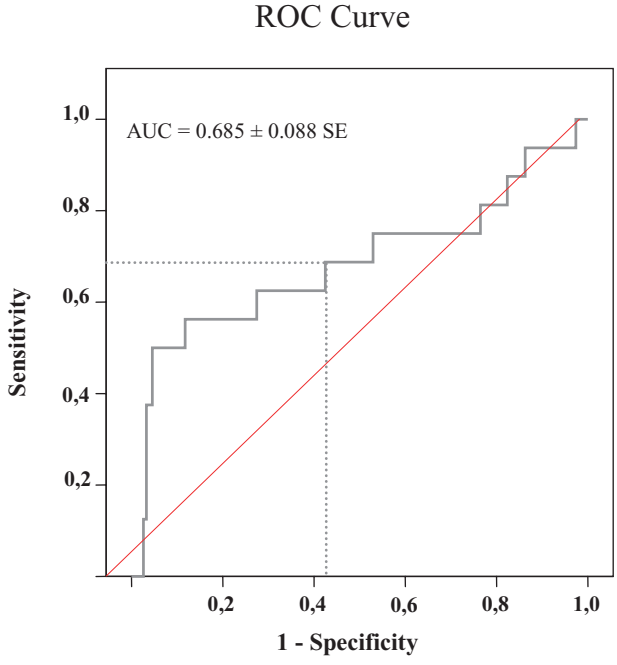


Figure 3 ROC curve showing the predictive value of serum ischemia-modified albumin (IMA) levels in the diagnosis of neonatal asphyxia.

associated with placental hypoxia and increased oxidative stress occurring concurrently with ischemia.[20–22] Papageorghiou *et al*. found that women who developed pre-eclampsia later had higher serum IMA levels in the first trimester than those with normal pregnancy.[20] Two studies have investigated the maternal IMA levels in pre-eclampsia.[21,23] Ustun *et al*., in contrast to results

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of van Rijn *et al*.,[23] demonstrated that IMA levels of pre-eclamptic women were significantly higher than normal controls and were correlated with the severity of pre-eclampsia;[21] however, none of these studies evaluated the IMA levels in newborns. In a limited study, Gugliucci *et al*. assessed cord blood IMA levels in neonates from complicated deliveries for the first time.[24] Likewise, in our study, we investigated cord blood IMA levels in newborns from complicated pregnancies. In addition, we compared them with cord blood IMA levels from healthy pregnancies. Our complicated group included newborns delivered from pregnancies with pre-eclampsia, diabetes mellitus and IUGR. Although there is no difference for the rate of newborns exposed to perinatal asphyxia between the groups, we found that IMA levels in the complicated group were significantly higher than in the control group.

A recently published report evaluating maternal IMA levels in GDM has shown that serum IMA levels were increased in these patients.[25] It was also found that there was a positive correlation between IMA and plasma glucose levels. These results were similar to those of several reports including diabetic non-pregnant patients.[26,27] Ukinc *et al*. have demonstrated that serum IMA levels were significantly associated with elevation of some markers such as microalbuminuria, hs-CRP related to endothelial dysfunction and damage, inflammation and reactive oxygen radicals produced as a result of ischemic events.[26] The pathophysiological findings may explain these results.

In the literature, there are no reports investigating the association of abnormal Doppler findings with serum levels of IMA. Therefore, we also compared normal and complicated pregnancies according to antenatal Doppler parameters and we investigated whether their IMA levels showed any correlation with Doppler measurements, especially in complicated pregnancies. We included Doppler investigations only in cases that had newborns with no clinical evidence of asphyxia, because we did not aim to evaluate the Doppler investigation as a predictor of perinatal asphyxia in this study.

Placental insufficiency is the main cause of fetal hypoxia and IUGR and activates fetal compensatory cardiovascular responses including redistribution of blood flow towards the brain, myocardium and the adrenal glands.[7] This response can be detected by using the C/P ratio. An abnormal C/P ratio has a more predictive value for perinatal adverse outcomes compared to the assessment of the UA and MCA.[12] Supporting these, we detected that the mean C/P ratio-PI values were significantly lower in complicated pregnancies than those of the controls. We also observed that the neonatal IMA levels were significantly higher in pregnancies with an abnormal C/P ratio than in the normal groups.

Differently, in a previous study, Iacovidou *et al*. did not find any difference in cord blood IMA levels between non-distressed IUGR and appropriate for gestational age neonates at term.[28] These conflicting results may be attributed to the fact that, in our study, the complicated pregnancy group did not encompass only IUGR cases. Also the authors explained their results without any evidence of myocardial damage in non-distressed term IUGR neonates. However, we investigated here the possible association of IMA levels and relatively chronic conditions such as pre-eclampsia or diabetes mellitus, and all of them were not as acute as myocardial infarction, but a microenvironment that could increase tissue hypoxia. As a result, we suggested that neonates from the complicated pregnancies presented elevated IMA levels that could indicate an important sub-clinical condition of a fetal or neonatal oxygenation insufficiency and a low-grade inflammatory status. Therefore, we suggested that the IMA level may even be a sensitive marker for newborns with abnormal Doppler findings without perinatal asphyxia or serious hypoxia.

In this study, neonatal IMA levels showed a negative correlation with the C/P ratio-PI, but it was not statistically significant. However, they have important positive correlations with the UA-PI. These results must be confirmed by other studies, including a larger series.

We also found a statistically significant adverse correlation between the IMA levels and birth weight, which is similar to the results of other studies.[23,24] We have also observed that the neonates with perinatal asphyxia have a lower birth weight than those of the non-asphyctic controls. We suggest that the results from both studies may be important for preterm deliveries and may be related to the previous reports, which have consistently demonstrated that increased reactive oxygen species (ROS) production occurs in preterm infants and is associated with a relative lack of antioxidant enzyme concentration and activity.[29] However, we showed that the elevation of IMA levels observed in neonates of complicated and asphyctic groups were found to be independent of their birth weights.

Cord blood IMA levels seem to be associated with the mode of delivery. Iacovidou *et al*. reported that

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IMA levels in cord blood were increased in cases of elective cesarean section compared to cases of vaginal delivery.[28] In our study, an upward trend was observed at the level of IMA in newborns from cesarean section, although the difference between the groups was not significant. These results might be influenced by the relatively small sample size, especially in cases of cesarean section. Also different from that study, the present report did not just include cases with elective cesarean sections.

There were several limitations of the study. We only studied neonatal cord blood IMA levels without the results of maternal IMA levels; therefore, we were unable to evaluate the relationship between neonatal and maternal IMA levels. We did not study IMA in conjunction with other markers, such as plasma glucose levels, because this study was designed before the published report that showed that plasma glucose levels affect serum IMA levels.[25] The study groups included a relatively small number of samples, therefore we could not give a cut-off value for IMA on prediction of asphyxia.

In conclusion, the cord blood IMA levels were increased in the newborns from complicated pregnancies regardless of perinatal asphyxia. Newborns with perinatal asphyxia had significantly higher serum IMA levels than the non-asphyctic ones. The newborns who underwent the 'brain-sparing effect' shown by an abnormal C/P ratio in antenatal Doppler examinations were associated with elevated cord blood IMA levels. We may accept elevated cord blood IMA levels as a novel, useful marker in perinatal asphyxia; however, the results of the present study are still preliminary and a future multi-institutional, prospective and controlled study is warranted.

Disclosure

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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